

Effects of Ondansetron and Granisetron on Postoperative Nausea and Vomiting in Adult Patients Undergoing Laparoscopic Cholecystectomy: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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ABSTRACT

Background: Postoperative nausea and vomiting (PONV) are common and potentially distressing adverse events (AEs) associated with surgery and anesthesia. In patients undergoing laparoscopic cholecystectomy (LC) without antiemetic prophylaxis, the incidence of PONV can be as high as 72%.

Objective: The aim of this study was to investigate the prophylactic antiemetic effects of ondansetron and granisetron in patients undergoing LC when these agents are administered before the end of surgery.

Methods: Patients classified by the American Society of Anesthesiologist's physical status as I or II who were scheduled for elective LC were included in this randomized, double-blind, placebo-controlled study. Anesthesia was induced with thiopental 5 mg/kg and fentanyl 2 µg/kg, and was maintained with isoflurane 1% to 3% in 50% oxygen and 50% nitrous oxide and fentanyl as needed. Approximately 20 to 30 minutes before the end of the surgery, the patients randomly received either IV ondansetron 100 µg/kg (group O), IV granisetron 40 µg/kg (group G), or normal saline (group P). Plasma levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined preoperatively and 24 hours postoperatively. The patients were observed for 24 hours for PONV and other possible AEs. Postoperative pain intensity was determined using a 10-cm visual analogue scale. Four-point satisfaction scores were determined at 24 hours.

Results: Ninety patients (69 women, 21 men) participated in the study. Demographic characteristics and operative data (duration of surgery and anesthesia and amount of intraoperative fentanyl) were similar in the 3 groups. The only AE reported by patients during the 24-hour observation period was nonsevere headache. The number of patients experiencing headache was simi-

lar in group P, group O, and group G (10 [33%] patients, 6 [20%], and 10 [33%], respectively). No significant changes were found in presurgical and postsurgical plasma levels of ALT and AST in any group. The mean (SD) satisfaction scores in group O and group G (3.0 [0.4] and 3.0 [0.6], respectively) were significantly higher than those in group P (2.5 [0.5]; both, $P < 0.01$). Immediately after surgery (period 0), significantly more patients in the placebo group (21 [70%]) experienced PONV compared with those in the ondansetron group (9 [30%]; $P < 0.05$) and the granisetron group (7 [23%]; $P < 0.01$). During the 24-hour observation period, a significantly greater number of patients in group P (18 [60%]) required a single dose of a rescue antiemetic drug compared with those in groups O and G (9 [30%] and 6 [20%], respectively; both, $P < 0.01$).

Conclusions: Patients administered ondansetron 100 µg/kg or granisetron 40 µg/kg 20 to 30 minutes before the end of LC had significantly higher PONV control during the 24-hour postoperative observation period than patients receiving placebo. However, there were no significant differences between the active treatment groups in the incidence of PONV, patient satisfaction, or AEs. (*Curr Ther Res Clin Exp.* 2007;68:303–312) Copyright © 2007 Excerpta Medica, Inc.

Key words: laparoscopic cholecystectomy, postoperative nausea and vomiting, ondansetron, granisetron.

INTRODUCTION

Postoperative nausea and vomiting (PONV) are common (overall incidence, 25%–30%) and possibly distressing adverse events (AEs) related to surgery and anesthesia.¹ In patients undergoing laparoscopic cholecystectomy (LC) without antiemetic prophylaxis, the incidence of PONV can be as high as 72%.² When compared with open cholecystectomy, LC has many advantages, such as a smaller scar, shorter hospital stay, and more rapid return to normal daily activities.³ However, the high incidence of PONV in patients not receiving antiemetic prophylaxis decreases the level of postoperative comfort that might be achieved with this minimally invasive surgery and makes antiemetic prophylaxis necessary.

To control PONV, traditional antiemetic drugs (eg, metoclopramide, droperidol, and promethazine) have been used successfully.^{1,4} However, these antiemetic drugs are associated with AEs (eg, sedation, dry mouth, and extrapyramidal symptoms).¹ The 5-hydroxytryptamine type 3 (5-HT₃) receptor antagonists have been shown to be effective in the prevention and treatment of PONV without significant AEs.^{1,2,5} In several studies,^{5–7} the selective 5-HT₃ receptor antagonists ondansetron and granisetron have been found to reduce the prevalence of PONV when administered prophylactically.

For PONV prophylaxis, both ondansetron and granisetron have been recommended to be administered at the start of anesthesia.^{1,8} However, other studies have found that antiemetic prophylaxis with these drugs was more efficient when they were administered at the end of surgery.^{9,10}

The aim of the present study was to investigate the antiemetic prophylactic effect of ondansetron and granisetron administered before the end of surgery to patients undergoing elective LC.

PATIENTS AND METHODS

The study was approved by the Faculty Ethics Committee of the Firat University School of Medicine, Elazig, Turkey. All patients provided written informed consent before participating in the study.

Consecutive adult patients of both sexes classified as American Society of Anesthesiologists physical status I or II¹ who were scheduled for elective LC were enrolled in this randomized, double-blind, placebo-controlled study. Patients with a history of PONV and/or motion sickness; patients who were pregnant, lactating, or menstruating; those with clinically notable gastrointestinal, cardiovascular, neurologic, renal, hepatic, or endocrinologic disease (eg, obesity, diabetes mellitus); and those who were receiving drugs with known antiemetic effects were excluded from the study. All patients were visited by a study investigator the day before surgery and were informed about the objective of the study and the use of a patient-controlled analgesia (PCA) pump.

Patients were randomized to receive ondansetron (group O), granisetron (group G), or placebo (group P). The investigator collecting the data and the patients were blinded to randomization. All study drugs (ondansetron 100 µg/kg, granisetron 40 µg/kg, and normal saline) were diluted by a nurse anesthetist to a fixed volume of 100 mL and marked with a coded label to ensure the double-blind nature of the study.

Patients were premedicated with IM midazolam 0.05 mg/kg 30 minutes before the induction of anesthesia. In the operating room, standard parameters (eg, electrocardiography, heart rate, noninvasive arterial blood pressure, temperature, pulse oximetry, and end-tidal carbon dioxide [CO₂]) were monitored. Normal saline (0.9%) was administered intravenously during surgery in all groups. Anesthesia was induced with thiopental 5 mg/kg and fentanyl 2 µg/kg. Vecuronium 0.2 mg/kg was administered to facilitate endotracheal intubation. After tracheal intubation, anesthesia was maintained with isoflurane 1% to 3% in a combination of 50% oxygen and 50% nitrous oxide. Supplements of IV fentanyl 1 µg/kg and IV vecuronium 2 mg were administered as needed. Ventilation was controlled mechanically and was adjusted to maintain the end-tidal CO₂ concentration at 30 to 40 mm Hg. After tracheal intubation, a nasogastric tube was inserted to remove gastric contents and air. All patients received a second-generation cephalosporin after tracheal intubation.

Approximately 20 to 30 minutes before the end of surgery, the patients received IV ondansetron 100 µg/kg,* granisetron 40 µg/kg,[†] or placebo (normal saline) over 10 minutes. At the end of surgery, the nasogastric tube was

*Trademark: Zofer® (Adeka, Samsun, Turkey).

[†]Trademark: Kytril® (Roche, Istanbul, Turkey).

removed and the anesthetic drugs were stopped. Patients received neostigmine 0.03 mg/kg and atropine 0.01 mg/kg to reverse residual neuromuscular blockade. All patients received fentanyl for postoperative analgesia via the IV PCA pump after a 25- μ g loading dose before tracheal extubation. The PCA pump was programmed to deliver a 0.2- μ g/kg bolus of fentanyl with a 15-minute lockout interval. Venous blood samples were drawn preoperatively and 24 hours postoperatively to determine plasma levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

All patients were observed in the recovery room during the first postoperative hour and then in the ward by the same investigator (A.Y.) who was blinded to the treatment groups. The investigator determined nausea-vomiting scores (0 = no nausea, 1 = nausea, 2 = retching and/or 1 vomitus, 3 = >1 vomitus) by direct questioning of the patients at the following postoperative times: 0 (when the patient first responded to a simple verbal order) and 1, 2, 4, 8, 12, and 24 hours. Patients with a PONV score of ≥ 2 received metoclopramide 10 mg IV as a rescue antiemetic. The investigator also assessed postoperative pain intensity using a 10-cm visual analogue scale (VAS) (0 = no pain to 10 = the worst pain). At 24 hours, the investigator recorded rescue antiemetic drug use, complete or incomplete response, total fentanyl consumption, and degree of satisfaction (1 = very unsatisfied, 2 = unsatisfied, 3 = satisfied, 4 = very satisfied). *Complete response* was defined as no PONV and/or no need for the rescue antiemetic drug.

Statistical Analysis

Statistical analyses were performed using analysis of variance with the Tukey honestly significant difference correction, Student *t* test, Mann-Whitney U test, independent-sample *t* test, and χ^2 test, where appropriate. All values were expressed as mean (SD), number (%), or median (range). $P < 0.05$ was considered significant. All the analyses were performed using the Statistical Package for Social Sciences version 12.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Ninety patients (69 women, 21 men) were included in the study. There were 30 patients in each group, and all of the patients completed the study. There were no significant differences between the 3 groups in regard to demographic characteristics, mean duration of surgery, mean duration of anesthesia, or intraoperative total fentanyl consumption (**Table I**).

The only AE reported by patients during the 24-hour observation period was nonsevere headache. The number of patients experiencing headache was similar in group P, group O, and group G (10 [33%], 6 [20%], and 10 [33%] patients, respectively).

All patients had postoperative pain scores ranging from 0 to 5 on the VAS. No differences were found in mean pain scores or postoperative total mean fentanyl consumption among the 3 groups (**Table II**).

Table I. Baseline demographic characteristics and operative data in adult patients undergoing laparoscopic cholecystectomy (N = 90).* Data are mean (SD) unless otherwise noted.

Variable	Ondansetron Group (n = 30)	Granisetron Group (n = 30)	Placebo Group (n = 30)
Age, y	39.1 (4.8)	41.6 (8.3)	40.6 (9.9)
Weight, kg	74.9 (10.0)	71.9 (8.8)	73.6 (13.0)
Height, cm	166.1 (7.1)	164.9 (7.1)	163.5 (8.1)
Sex, no. (%)			
Female	24 (80)	22 (73)	23 (77)
Male	6 (20)	8 (27)	7 (23)
Duration of surgery, min	76.3 (18.6)	79.0 (19.1)	71.8 (23.5)
Duration of anesthesia, min	89.5 (19.7)	92.1 (19.8)	85.5 (32.3)
Intraoperative fentanyl, µg	145.5 (48.7)	156.5 (32.4)	154.1 (46.5)

*No significant between-group differences were found.

Table II. Postoperative data and plasma levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in adult patients undergoing laparoscopic cholecystectomy (N = 90).

Variable	Ondansetron Group (n = 30)	Granisetron Group (n = 30)	Placebo Group (n = 30)
Fentanyl, mean (SD), µg	107.5 (22.8)	118.5 (22.9)	113.3 (29.5)
Rescue antiemetic, no. (%)	9 (30)*	6 (20)*	18 (60)
Complete response, no. (%)	21 (70) [†]	23 (77) [†]	9 (30)
Satisfaction score, [‡] median (range)	3.0 (2–4)*	3.0 (2–4)*	2.5 (2–3)
Headache, no. (%)	6 (20)	10 (33)	10 (33)
Preoperative, mean (SD), IU/L			
AST	20.9 (10.0)	23.3 (11.6)	25.5 (14.3)
ALT	24.2 (10.0)	30.3 (21.3)	27.3 (15.6)
Postoperative, mean (SD), IU/L			
AST	38.1 (22.6)	29.1 (14.4)	35.7 (8.7)
ALT	40.5 (20.8)	35.4 (18.9)	40.8 (11.9)

* $P < 0.01$ versus placebo.

[†] $P < 0.001$ versus placebo.

[‡]Scale: 1 = very unsatisfied; 2 = unsatisfied; 3 = satisfied; 4 = very satisfied.

Between-group differences in both preoperative and postoperative plasma levels of ALT and AST were not statistically significant. The mean (SD) satisfaction scores in group O and group G (3.0 [0.4] and 3.0 [0.6], respectively) were significantly higher than in group P (2.5 [0.5]; both, $P < 0.01$). In the first 24 hours after surgery, the number of patients with complete response in groups O and G was significantly higher (21 [70%] and 23 [77%], respectively) compared with that of placebo (9 [30%]; both, $P < 0.001$) (Table II).

Immediately after surgery (period 0), significantly more patients in the P group (21 [70%]) had PONV compared with the O group (9 [30%]; $P < 0.05$) and the G group (7 [23%]; $P < 0.01$). During the first hour after surgery, significantly more patients in group P (21 [70%]) had PONV than in groups O and G (2 [7%] and 6 [20%]; both, $P < 0.001$) (Table III). In group P, 7 patients displayed only nausea 4 hours postoperatively and 6 patients displayed only nausea at 8 hours. No patient in group P experienced postoperative vomiting after 1 hour. No patient in group O or group G experienced PONV after 1 hour. Persistent vomiting was not observed in any group.

During the 24-hour observation period, a significantly higher number of patients in group P (18 [60%]) required a single dose of a rescue antiemetic drug compared with groups O and G (9 [30%] and 6 [20%]; both, $P < 0.01$) (Table II).

The prevalence and severity of PONV, the number of patients requiring a dose of rescue antiemetic drug, and the number of patients who had a complete response were similar between the ondansetron and granisetron groups.

Table III. The incidence and severity of postoperative nausea and vomiting in adult patients undergoing laparoscopic cholecystectomy (N = 90).

Postoperative Hour	Ondansetron Group (n = 30)		Granisetron Group (n = 30)		Placebo Group (n = 30)	
	No. (%)	Score,* mean (SD)	No. (%)	Score,* mean (SD)	No. (%)	Score,* mean (SD)
0	9 (30)	0.6 (0.9) [†]	7 (23)	0.4 (0.8) [‡]	21 (70)	1.2 (0.8)
1	2 (7)	0.1 (0.4) [§]	6 (20)	0.3 (0.6) [§]	21 (70)	1.3 (0.9)
2	0	0 [§]	0	0 [§]	10 (33)	0.3 (0.4)
4	0	0 [‡]	0	0 [‡]	7 (23)	0.2 (0.4)
8	0	0 [‡]	0	0 [‡]	6 (20)	0.2 (0.4)
12	0	0	0	0	0	0
24	0	0	0	0	0	0

*Scale: 0 = no nausea; 1 = nausea; 2 = retching and/or 1 vomitus; 3 = >1 vomitus.

[†] $P < 0.05$ versus placebo.

[‡] $P < 0.01$ versus placebo.

[§] $P < 0.001$ versus placebo.

DISCUSSION

PONV are observed with all types of surgery and in all patient populations when prophylactic antiemetic drugs are not used.¹ The prevalence of PONV in patients undergoing LC without antiemetic prophylaxis ranges from 43% to 72%.^{2,12} In many studies, the prevalence of PONV has been found to decrease significantly with antiemetic prophylaxis.^{2,6,7} Traditional antiemetic drugs (eg, droperidol and metoclopramide) may be associated with AEs (eg, sedation, dry mouth, and extrapyramidal symptoms). The 5-HT₃ receptor antagonists are not associated with such AEs, and they have more effective antiemetic activity.^{1,2,5} Therefore, 5-HT₃ receptor antagonists are used to prevent and treat PONV after a variety of surgical procedures.^{1,5,7} Ondansetron, the first selective 5-HT₃ receptor antagonist used for the prevention of PONV, and granisetron, another selective 5-HT₃ receptor antagonist, have been found to be well tolerated and highly effective in preventing and treating PONV.^{5-7,12}

The timing of prophylactic antiemetic management might be important. In some studies, ondansetron and granisetron were administered at the start of anesthesia for PONV prophylaxis.^{1,6,8,12} However, 1 study found it was more effective to administer ondansetron 4 mg IV at the end of surgery than at the start of anesthesia (complete responses, 74% and 71%, respectively; $P < 0.05$).⁹ Administering these antiemetic drugs at the end of surgery had additional benefits, including increased effectiveness of lower doses and greater patient satisfaction.^{9,13}

Ondansetron reaches peak plasma concentration in 20 to 30 minutes after intravenous administration.⁸ In healthy volunteers, granisetron has also been shown to reach peak plasma concentrations 30 minutes after intravenous administration.⁸ Therefore, intravenous administration of either drug 20 to 30 minutes before extubation may provide sufficient postoperative antiemetic effect. However, ondansetron and granisetron may not be sufficiently effective when administered at the end of surgery or just before extubation. So et al¹⁴ found that patients administered a single 4-mg dose of IV ondansetron at the end of LC (just before tracheal extubation) had similar PONV scores to the placebo group at the end of the study. The authors concluded that ondansetron 4 mg after LC did not reduce the prevalence of nausea and vomiting. Quaynor and Raeder⁴ administered patients IV metoclopramide 20 mg or ondansetron 8 mg after surgery. Despite the high doses, the overall prevalence of PONV was high (47% with metoclopramide and 43% with ondansetron). In both studies, the high rate of PONV might be attributed to the delay in the administration of antiemetic drugs. Because the mean (SD) plasma elimination $t_{1/2}$ of both ondansetron and granisetron are relatively short (~2.8 [0.6] and ~3.1 [1.2] hours, respectively),^{15,16} patients may need to receive a repeat dose. However, for short surgical procedures, these drugs may be administered during anesthesia induction.

In the present study, 70% of patients in the placebo group experienced PONV during the 24-hour postsurgical observation period, while PONV was 30% with

ondansetron 100 µg/kg and 23% with granisetron 40 µg/kg administered before the end of LC. No significant differences were found between the groups in the risk factors for PONV (eg, patient demographic characteristics, operative procedure, anesthesia administration procedure, anesthetics used, and intraoperative and postoperative analgesic consumption). Therefore, we believe that the differences in PONV control observed were associated with the antiemetic drugs used.

The adult dose of ondansetron recommended to prevent PONV is 4 mg.⁸ However, in a randomized, double-blind, placebo-controlled study of 2119 patients (aged ≥12 years), Kovac et al¹⁷ found that the 4-mg dose of ondansetron was not effective. In a meta-analysis of 53 trials with 7177 patients receiving 24 different ondansetron formulations, Tramer et al¹⁸ recommended IV ondansetron 8 mg for PONV prophylaxis. In a randomized, double-blind comparison study by Zarate et al,¹³ outpatients undergoing otolaryngologic procedures received IV ondansetron 4 or 8 mg <30 minutes before the end of surgery. The 8-mg dose was not found to be significantly more effective than ondansetron 4 mg. The ondansetron dose used in the present study was within the recommended range (4–8 mg) for PONV prevention.

To prevent PONV after various surgical procedures, the optimal dose of granisetron was found to be 40 µg/kg^{19,20}; higher doses have not been found to be more effective.^{19,21} Similarly, granisetron 40 µg/kg was found to be the minimum effective dose for preventing PONV in patients undergoing LC.¹² Therefore, granisetron 40 µg/kg was used in this study.

A randomized, double-blind, placebo-controlled study² comparing the antiemetic effects of ondansetron and granisetron in PONV found no difference in effectiveness between the 2 drugs. A dose of IV granisetron 3 mg was found to provide no more effective antiemetic prophylaxis than ondansetron 4 mg in patients undergoing LC. A 2003 study²² found granisetron to be superior to ondansetron in the prevention of PONV after outpatient gynecologic laparoscopic surgery (administered 2 minutes before induction of general anesthesia); granisetron 2 mg IV was found to be more effective than ondansetron 4 mg IV (emetic episodes were observed in 7% of patients who had received intravenous granisetron and 20% in those who had received ondansetron). In the study by Naguib et al,² a dose of IV granisetron 3 mg was comparable to ondansetron 4 mg with regard to effective antiemetic prophylaxis in patients undergoing LC.

The most frequently reported AEs of 5-HT₃ receptor antagonists are headache (<2%) and dizziness (12%).^{4,5,8} Transient elevated plasma levels of AST and ALT without clinically significant hepatic changes have also been reported.⁸ In 1 study,¹ 5-HT₃ receptor antagonists were not found to affect liver function tests. Another study¹⁰ found preoperative and postoperative plasma aminotransferase activities to be similar and also found no difference compared with placebo. In the present study, no significant differences were found in preoperative and postoperative plasma aminotransferase levels. The only patient-reported AE was nonsevere headache; the prevalence of headache was similar in the 3 groups.

Limitations

This study included a relatively small sample size to identify differences in the prevalence of PONV. However, when the previous studies are taken into account, we believe that the sample size we used was sufficient. Another limitation was the lack of medication groups at the start of anesthesia to use for comparisons. Comparisons were based on the placebo group and the previous studies.

CONCLUSIONS

Patients administered ondansetron 100 µg/kg or granisetron 40 µg/kg 20 to 30 minutes before the end of LC had significantly higher PONV control during the 24-hour postoperative observation period than patients administered placebo. However, there were no significant differences between the active treatment groups in the prevalence of PONV, patient satisfaction, or AEs. No serious AEs were observed with either drug.

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